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DOCKET NO. 2629-4005US1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s) : Attila T. LÖRINCZ, et al. Group Art Unit: 1631
Serial No : 09/210,031 Examiner: BRUSCA, J.
Filed : December 11, 1998
For : UNIVERSAL COLLECTION MEDIUM

DECLARATION UNDER 37 C.F.R. §1.132

Commissioner of Patents
Washington, D.C. 20231

Sir:

This is a Declaration filed pursuant to 37 C.F.R. §1.132.

I, the undersigned, Attila T. Lörincz, Ph.D., declare and state that:

1. I am a co-inventor of the subject patent application having serial no.

09/210,031.

2. My education and professional experience as an expert in the area of nucleic acid chemistry and analysis are set forth on the attached copy of my Curriculum Vitae.

3. As stated on my Curriculum Vitae attached herewith, my area of expert training and experience is in nucleic acid chemistry, in the analysis of nucleic acids in biological samples, and in the use of such nucleic acid analyses to develop diagnoses and prognoses concerning diseases related to the organism from which the nucleic acid was obtained.

4. I understand that the Examiner considers the composition described in the above-identified application obvious in view of the composition reported at column 6, lines 8-61 and in Example 4 of Dunphy U.S. Patent No. 5,679,333 ("333 patent").

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5. It is my opinion, as an expert in the field of nucleic acid chemistry analysis, that the composition described in Dunphy does not teach or suggest the compositions described in the above-identified application because the direct analysis of cells by both cytological analysis and molecular analysis of DNA, RNA, or protein is not possible using the compositions of Dunphy.

6. To support this position, I present evidence herein establishing that the Dunphy composition of Example 4 does not properly preserve DNA and RNA. The data demonstrate that the Dunphy composition cannot provide direct molecular analysis of cells according to the subject claims because the Dunphy composition quickly degrades the nucleic acids in the sample.

7. The following experimental study measures the stability of nucleic acids in our universal collection medium (UCM) composition as compared to nucleic acid samples in the Dunphy composition over a period of four weeks. In this study, eight (8) different formulations were evaluated for their ability to maintain cellular DNA and cellular RNA. This study demonstrates that Dunphy's formulations, with or without the addition of EDTA or other modifications, are not suitable storage media for the analysis of cellular nucleic acids. Low levels of DNA or RNA detection in Dunphy's formulations even in the Day 1 timepoint suggest that Dunphy's tissue fixative media are not appropriate for analyzing nucleic acids. All of the applicants' (UCM) formulations evaluated in this study are suitable media for the storage and subsequent detection of cellular nucleic acids.

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8. The 8 formulations, applicants' 1-3 and Dunphy's 4-8, were prepared as follows and used in the molecular analyses described below:
Formulation No. 1 is formulation 130 from the UCM I patent application (USSN: 09/210,031; "UCM I"). It shows the ability of the UCM formulation containing glutaraldehyde to preserve cellular DNA and RNA.

Butanol	7% v/v
Sodium Azide	0.05% w/v
EDTA	0.18% w/v (= 5 mM)
Glutaraldehyde-Sodium-Bisulfate (G-S-B)	2.5% w/v
Acetic Acid	0.11% v/v
pH 3.7	

Formulation No. 2, similar to Formulation No. 1 above, but without the addition of glutaraldehyde, shows the need for a cross-linker in the UCM formulation.

Butanol	7% v/v
Sodium Azide	0.05% w/v
EDTA	0.18% w/v (= 5 mM)
Acetic Acid	0.11% v/v
pH 3.7	

Formulation No. 3, UCM similar to Formulation No. 1 above, but without the addition of EDTA, shows the need for a chelating agent in "UCM I," to assist in the inhibition of RNA and DNA degradation.

Butanol	7% v/v
Sodium Azide	0.05% w/v
Glutaraldehyde-Sodium-Bisulfate (G-S-B)	2.5% w/v
Acetic Acid	0.11% v/v
pH 3.7	

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Formulation No. 4 is Dunphy's tissue fixative from Example 4 of the Dunphy '333 patent. It is one of five variations of Dunphy's media that tests its ability to preserve cellular DNA and RNA.

Ethanedial (Glyoxal)	3.75% v/v
Ethanol	20% v/v
PEG (MW 8000)	2.0% w/v
Ethylene Glycol	0.75% v/v
Ethanoic Acid	0.75% v/v
Dimethyl Sulfoxide (DMSO)	0.0275% v/v

Formulation No. 5 of Dunphy's tissue fixative is similar to Formulation No. 4 above with the addition of EDTA at the concentration used in the Dunphy pre-injection and arterial injection fluids. The Examiner stated that it would have been obvious to add EDTA in formulations of Dunphy's media. This shows that EDTA does not improve nucleic acid stability. See Tables 2 and 4.

Ethanedial (Glyoxal)	3.75% v/v
Ethanol	20% v/v
PEG (MW 8000)	2.0% w/v
Ethylene Glycol	0.75% v/v
Ethanoic Acid	0.75% v/v
Dimethyl Sulfoxide (DMSO)	0.0275% v/v
EDTA	0.08% w/v

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Formulation No. 6 of Dunphy's tissue fixative is similar to Formulation No. 4 above with the addition of EDTA at the concentration used in the UCM formulations. This shows that EDTA does not improve nucleic acid stability, regardless of its concentration. See Tables 2 and 4.

Ethanedial (Glyoxal)	3.75% v/v
Ethanol	20% v/v
PEG (MW 8000)	2.0% w/v
Ethylene Glycol	0.75% v/v
Ethanoic Acid	0.75% v/v
Dimethyl Sulfoxide (DMSO)	0.0275% v/v
EDTA	0.18% w/v (= 5 mM)

Formulation No. 7 of Dunphy's tissue fixative is similar to Formulation No. 4 above with the addition of phosphate buffer to raise the pH to approximately 7.0. The Dunphy patent states that although the solution typically has an acidic pH, it may be buffered to a substantially neutral pH. Addition of the phosphate buffers raises the pH of the solution to a neutral range. See Tables 2 and 4.

Ethanedial (Glyoxal)	3.75% v/v
Ethanol	20% v/v
PEG (MW 8000)	2.0% w/v
Ethylene Glycol	0.75% v/v
Ethanoic Acid	0.75% v/v
Dimethyl Sulfoxide (DMSO)	0.0275% v/v
Acid Sodium Phosphate Monohydrate	0.4% w/v
Disodium Phosphate (Anhydrous)	0.65% w/v
pH 6.8-7.8	

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Formulation No. 8 of Dunphy's tissue fixative is similar to Formulation No. 4 above with the addition of phosphate buffer to raise the pH to an approximately neutral range, as well as the addition of EDTA. The addition of EDTA at the concentration used in the Dunphy pre-injection and arterial injection fluids shows that it does not improve nucleic acid stability when included in a neutral formulation of Dunphy's media. See Tables 2 and 4.

Ethanedial (Glyoxal)	3.75% v/v
Ethanol	20% v/v
PEG (MW 8000)	2.0% w/v
Ethylene Glycol	0.75% v/v
Ethanoic Acid	0.75% v/v
Dimethyl Sulfoxide (DMSO)	0.0275% v/v
Acid Sodium Phosphate Monohydrate	0.4% w/v
Disodium Phosphate (Anhydrous)	0.65% w/v
EDTA	0.08% w/v
pH 6.8-7.8	

9. Cultured, Human Papilloma Virus (HPV)-16-positive CaSki cells and HPV-negative Jurkat cells were used to examine whether or not the Dunphy compositions preserve and make possible the direct analysis of nucleic acid.

10. Samples for DNA analysis were prepared as follows: 1.5 mL bulk samples were made from which 200 μ L, single use aliquots were made. The aliquots were stored at room temperature until tested.

Positive Control: HPV16 plasmid DNA was spiked into each of the eight formulations at a final concentration of 50 pg/mL.

Negative Control: A culture of HPV negative cells (obtained from ATCC cat #. TIB-152) was isolated and spiked into each of the eight

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formulations at a concentration of 10^6 cells/mL of each formulation.

CaSki Cells: A culture of HPV positive cells (obtained from ATCC cat# CRL-1550) was isolated and spiked into the eight formulations at two different concentrations, 10^4 and 10^5 cells/mL.

11. Samples for RNA Analysis were prepared as follows: 1 mL bulk samples were made from which 40 μ L, single use aliquots were made. The aliquots were stored at room temperature until tested.

Positive Control: HPV16 *in vitro* transcribed RNA was spiked into each of the eight formulations at a final concentration of 11 pg/mL.

Negative Control: A culture of HPV negative cells (obtained from ATCC cat #. TIB-152) was isolated and spiked into each of the eight formulations at a concentration of 10^6 cells/mL of each formulation.

CaSki Cells: A culture of HPV positive cells (obtained from ATCC cat# CRL-1550) was isolated and spiked into the eight formulations at two different concentrations, 10^5 and 10^6 cells/mL.

12. Samples were prepared and aliquotted, stored overnight at room temperature and tested the following day. The Day 1 time point reflects the handling of a true patient sample. Samples are usually collected and shipped to a testing facility. Therefore, the earliest that a patient sample could be tested would be 12 to 24 hours after the sample was collected.

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13. The estimated time for conducting DNA and RNA stability assays was 5-6 hours for 2 people and was conducted as follows:

- Isolating cell cultures (1 hour)
- Counting cell cultures (15 minutes)
- Spiking cells into formulations (1 hour)
- Spiking control into formulation (15 minutes)
- Aliquotting
- Vortexing (30 sec per sample, 130 samples, ~ 1.5 hours)
- Pipetting into labeled tubes
- Organizing samples for testing (30 minutes)

14. The direct analyses of nucleic acids were conducted by following the method for detecting DNA and RNA by the Digene Hybrid Capture (HC) method, described in WO 93/10263 by Digene Corporation.

15. The UCM DNA stability assay (estimated assay time: 4-5 hrs) was performed by first preparing the plate controls according to the package insert. Denaturation reagent (Sodium hydroxide; 100 μ l) was added to each of the samples and all of the samples were denatured at 65°C for 45 minutes. After incubation, the samples were neutralized by adding 100 μ l of probe, containing an RNA probe specific to genomic HPV DNA, and transferring 100 μ l of each sample in triplicate to the hybridization plate. Hybridization occurred at 65°C for 1 hour. Anti-hybrid detection antibody, DR-1, (25 μ l) was added to each well and all 125 μ l of the mixture was transferred to the capture plate containing strepavidin-coated microplate coated with anti-hybrid polyclonal antibody. The sample was captured for 1 hour at room

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temperature while shaking at 1100 rpm. The plate was then washed and blotted. The chemiluminescent substrate detection reagent was added to the plate which was then covered and stored in the dark for 30 minutes. The plate was then read on a luminometer. The data were then expressed as a signal-to-noise ratio. These assays test the efficacy of preservation media as specific signal is obtained only when DNA or RNA is not degraded, since signal is contingent upon the hybridization of probes to non-degraded DNA or RNA.

16. The UCM RNA stability assay was performed by first adding an equal volume of freshly prepared 2X SDS-based lysis buffer plus proteinase K to each sample. Lysis occurred at 37°C for 30 minutes in a waterbath. Lysis buffer without Proteinase K and without calcium (1X; 160 µl) was added to each of the samples. Plate control (480 µl) was added to the samples and vortexed well. Each sample (60 µl) was aliquotted in triplicate on the hybridization plate. The UCM probe, containing single-stranded DNA biotinylated probe specific for HPV E6 and E7 RNA (50 µl) was then added to each well and hybridized for 2 hours in a 65°C heat block. DR-1 (25 µl) was added to each well and the entire sample was transferred to the streptavidin capture plate. Capture occurred at room temperature for 1 hour while shaking at 1100 rpm. The plate was then washed and blotted dry. The plate was then heat washed at 53°C for 45 minutes, followed by washing and blot drying as previously described. Detection reagent to the plate which was then covered and stored in the dark for 30 minutes. The plate was then read on a luminometer with a standard setting. The data were then expressed as a signal-to-noise ratio. These assays test the efficacy of

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preservation media as specific signal is obtained only when DNA or RNA is not degraded, since signal is contingent upon the hybridization of probes to non-degraded DNA or RNA.

17. On the day of testing, a single tube for each of the controls and cellular samples was used in each assay. Each tube contained sufficient sample for triplicate assays of the nucleic acid targets. The raw data are represented in Relative Light Units (RLUs) that were collected on Digene's standard Luminometer. Hybrid Capture nucleic acid assays normally have less than or equal to 25% coefficient of variation (%CV) within triplicate assays. When the %CV is greater than 25%, one outlier may be eliminated. The compiled data are presented as signal/noise (S/N) where the signal represents the average RLU of the triplicate assays divided by the noise obtained from a buffer only, negative control.

18. Tables 1 and 2 and Figures 1A-1D set forth the data resulting from the DNA stability assay experiments.

	STORAGE MEDIA #	POSITIVE CONTROLS (50PG/ML HPV16 DNA)				HPV NEGATIVE CELLULAR SAMPLES (10 ⁶ JURKAT CELLS/ML)			
		DAY 1	WEEK 2	WEEK 3	WEEK 4	DAY 1	WEEK 2	WEEK 3	WEEK 4
UCMI	1	93.2	46.9	33.6	24.9	1.8	1.4	1.3	1.5
	2	82.8	9.3	6.1	3.2	1.7	2.0*	1.5	1.4
	3	75.0	28.5	18.1	11.3	1.4	1.4	1.2	1.2
DUNPHY'S	4	1.0	1.0	0.0	0.9	1.0	1.1	0.0	0.9
	5	0.9	0.6	1.1	1.0	0.9	0.8	1.2	0.9
	6	0.9	2.8*	1.0	1.2	0.8	0.9	1.0	1.0
	7	1.0	1.0	1.4	1.0	0.9	1.0	1.3	1.0
	8	0.9	0.9	0.9	0.9	1.3	1.0	1.2	1.2

* Indicates outliers that are the result of incomplete denaturation of the samples.

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Table 1: The Signal to Noise (S/N) values for the Hybrid Capture II HPV DNA assays performed at each of the nucleic acid study time points for the positive and HPV negative controls. The storage media number refers to the formulation number identified previously. Media 1-3 are UCM formulations, while media 4-8 are Dunphy's formulations.

FIGURE 1(A):

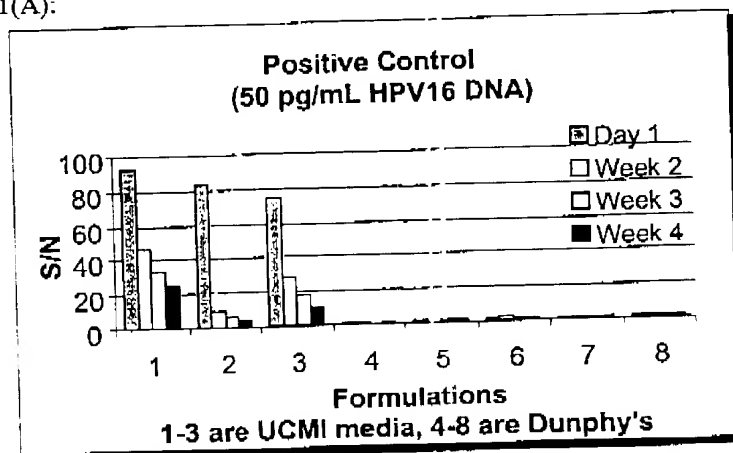


Figure 1(A) shows the results of the Signal to Noise (S/N) values (y-axis) of the positive control in each of the eight formulations, where the Hybrid Capture II HPV DNA assays were performed at each of the nucleic acid study time points.

FIGURE 1(B):

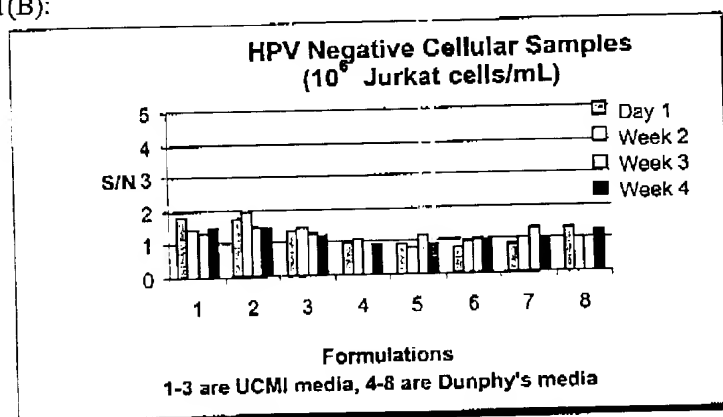


Figure 1(B) shows the results of the Signal to Noise (S/N) values (y-axis) of the negative control (10⁶ Jurkat cells/mL) in each of the eight formulations, where the Hybrid Capture II HPV DNA assays were performed at each of the nucleic acid study time points.

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	STORAGE MEDIA #	HPV POSITIVE CELLULAR SAMPLES (10 ⁴ CaSKI CELLS/ML)				HPV POSITIVE CELLULAR SAMPLES (10 ⁵ CaSKI CELLS/ML)			
		DAY 1	WEEK 2	WEEK 3	WEEK 4	DAY 1	WEEK 2	WEEK 3	WEEK 4
UCM 1	1	25.4	46.0	38.5	40.8	312.1	365.2	438.1	270.0
	2	99.4	57.8	50.4	37.0	652.7	621.7	569.2	356.0
	3	31.8	28.2	29.4	22.7	223.4	325.0	242.6	180.2
DUNPHY'S	4	1.0	1.0	0.0	0.9	1.0	1.1	0.0	1.0
	5	1.0	0.5	1.1	1.0	0.9	0.6	1.1	1.0
	6	0.9	1.1	0.9	1.1	0.8	1.0	0.9	1.1
	7	0.9	1.0	1.3	1.0	0.9	1.1	1.4	1.1
	8	1.1	1.0	1.0	1.2	1.2	1.0	1.0	1.3

* Indicates outliers that are the result of incomplete denaturation of the samples.

Table 2: The Signal to Noise (S/N) values for the Hybrid Capture II HPV DNA assays performed at each of the nucleic acid study time points for the HPV positive samples using 10⁴ or 10⁵ CaSki cells. The storage media number refers to the formulation number identified in the materials and methods. Media 1-3 are UCM formulations, while media 4-8 are Dunphy's formulations.

FIGURE 1(C):

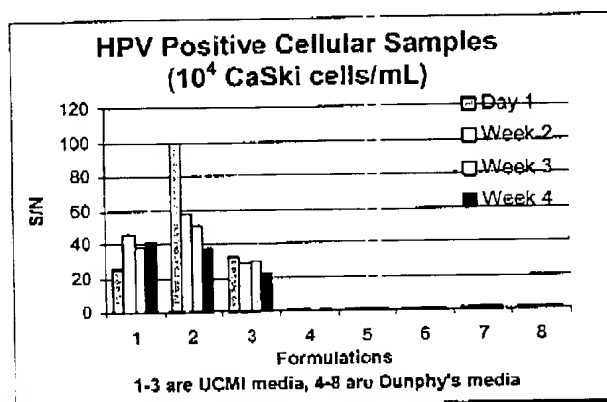


Figure 1(C) shows the results of the Signal to Noise (S/N) values (y-axis) of the HPV positive samples (10⁴ CaSki cells/mL) in each of the eight formulations, where the Hybrid Capture II HPV DNA assays were performed at each of the nucleic acid study time points.

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FIGURE 1(D):

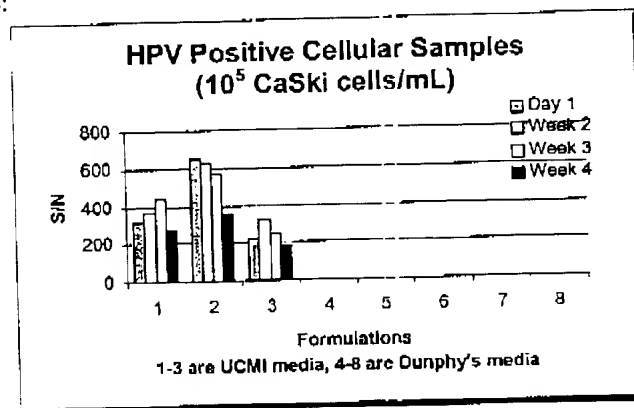


Figure 1(D) shows the results of the Signal to Noise (S/N) values (y-axis) of the HPV positive samples (10⁵ CaSki cells/mL) in each of the eight formulations, where the Hybrid Capture II HPV DNA assays were performed at each of the nucleic acid study time points.

19. The UCM data from the DNA stability assays provide the following results: UCM Formulation Nos. 1-3 were evaluated for the use of glutaraldehyde and EDTA to stabilize cellular nucleic acids in UCM formulations. EDTA variations were introduced to determine if the addition of a chelating agent to Dunphy's media would enhance nucleic acid stability in the media. The positive control HPV16 plasmid DNA spiked into these three formulations gave robust signals at the Day 1 time point, but lost signal over time (Figure 1). These results were expected since UCM formulations are acidic and plasmid DNA is known to be unstable in an acidic environment¹. The negative control samples had consistent negative signals, as determined as a S/N less than 2.0. As seen in Table 1, there are a few instances where the S/N for the negative control is at or greater than 2.0 (Formulation No. 2, Week 2).

¹ JJ Green, Rao VB. Recombinant DNA Principles and Methodologies. Marcel Dekker, USA 1998, p.23.

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This is the result of an incomplete denaturation step for these samples. The denaturation step is crucial for lysing the cells and destroying cellular RNA. If RNA destruction is incomplete, the naturally occurring DNA:RNA hybrids may be captured and detected in this assay (Table 1, Figure 1). The HPV positive cellular samples gave robust signals for these three formulations. The removal of EDTA in Formulation No. 3 resulted in a general decrease in signal throughout the study indicating that the EDTA is essential for the stability of cellular DNA. The absence of the cross-linking agent, glutaraldehyde-sodium-bisulfate (GSB), in Formulation No. 2 gave a stronger signal than Formulation Nos. 1 and 3 which have the agent.

20. The Dunphy data from the DNA stability assays provide the following results: Several different Dunphy formulations (Formulation Nos. 4-8) were examined for their ability as a storage media for cellular DNA and RNA. EDTA was added to Formulation Nos. 5, 6 and 8, and Formulation Nos. 7 and 8 were neutralized in an attempt to stabilize DNA. Dunphy's media are not suitable for nucleic acid storage because they failed in every formulation and at every time point to preserve DNA (Tables 1 and 2; Figures 1A-1D). The addition of EDTA to Dunphy's Formulation Nos. 5, 6, or 8 had no effect on the stability of nucleic acids. See Tables 1 and 2. Neutralizing the pH of Dunphy's media (Formulation Nos. 7 and 8) also failed to stabilize the cellular DNA.

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21. Tables 3 and 4 and Figures 2A-2D set forth the data resulting from the RNA stability analyses.

	STORAGE MEDIA #	POSITIVE CONTROLS (11 PG/ML HPV16 RNA)				HPV NEGATIVE CELLULAR SAMPLES (10 ⁶ JURKAT CELLS/ML)			
		DAY 1	WEEK 2	WEEK 3	WEEK 4	DAY 1	WEEK 2	WEEK 3	WEEK 4
UCM I	1	5.6	1.2	1.1	1.0	1.1	1.0	1.2	1.7
	2	35.9	31.5	30.8	27.0	1.0	1.0	1.1	1.1
	3	7.8	1.3	0.8	1.4	1.0	1.0	0.8	0.9
DUNPHY'S	4	1.0	0.9	1.5	0.9	0.9	0.8	1.0	1.2
	5	1.2	0.6	1.2	0.8	1.1	0.6	0.8	1.0
	6	0.9	1.7	1.2	0.9	1.1	1.2	1.2	0.9
	7	1.0	1.1	1.1	1.1	1.1	1.2	0.9	1.0
	8	0.9	1.2	0.8	1.4	1.1	1.1	0.9	1.2

Table 3: The Signal to Noise (S/N) values for the Hybrid Capture II HPV RNA assays performed at each of the nucleic acid stability study time points for the HPV positive samples using 10⁴ or 10⁵ CaSki cells. The storage media number refers to the formulation number identified previously. Media 1-3 are UCM formulations, while media 4-8 are Dunphy's formulations.

FIGURE 2(A):

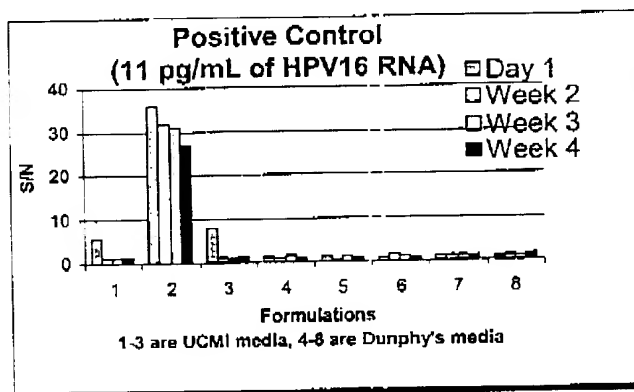


Figure 2(A) shows the results of the Signal to Noise (S/N) values (y-axis) of the positive control in each of the eight formulations, where the Hybrid Capture II HPV RNA assays were performed at each of the nucleic acid study time points.

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FIGURE 2(B):

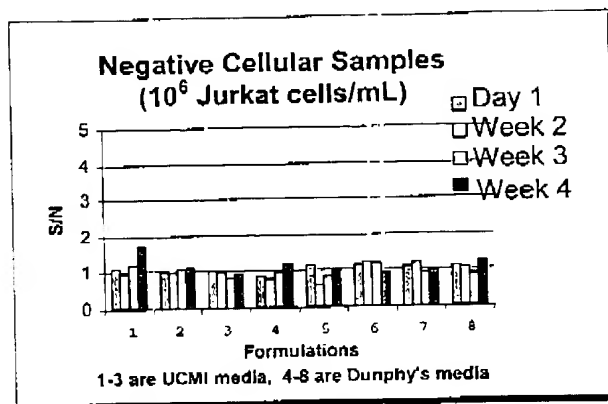


Figure 2(B) shows the results of the Signal to Noise (S/N) values (y-axis) of the negative control in each of the eight formulations, where the Hybrid Capture II HPV RNA assays were performed at each of the nucleic acid study time points.

	STORAGE MEDIA #	HPV POSITIVE CELLULAR SAMPLES (10 ⁵ CASKI CELLS/ML)				HPV POSITIVE CELLULAR SAMPLES (10 ⁶ CASKI CELLS/ML)			
		DAY 1	WEEK 2	WEEK 3	WEEK 4	DAY 1	WEEK 2	WEEK 3	WEEK 4
UCM I	1	3.6	3.7	3.9	3.8	29.9	25.0	28.5	23.8
	2	2.7	2.3	2.1	2.1	21.0	21.8	11.4	14.7
	3	4.6	3.2	3.3	3.3	19.8	27.8	21.8	22.0
DUNPHY'S	4	0.9	0.9	0.9	1.2	0.9	0.8	1.1	1.4
	5	1.2	0.6	1.3	1.1	1.1	0.5	1.2	1.0
	6	0.9	1.3	1.0	1.0	1.0	1.0	1.2	1.0
	7	1.2	1.3	0.8	1.0	1.2	1.2	1.2	1.3
	8	1.2	1.3	0.8	1.1	0.7	1.1	0.8	1.2

Table 4: The Signal to Noise (S/N) values for the Hybrid Capture II HPV RNA assays performed at each of the nucleic acid study time points for the HPV positive samples using 10⁵ or 10⁶ CaSki cells. The storage media number refers to the formulation number identified previously. Media 1-3 are UCM formulations, while media 4-8 are Dunphy's formulations.

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FIGURE 2(C):

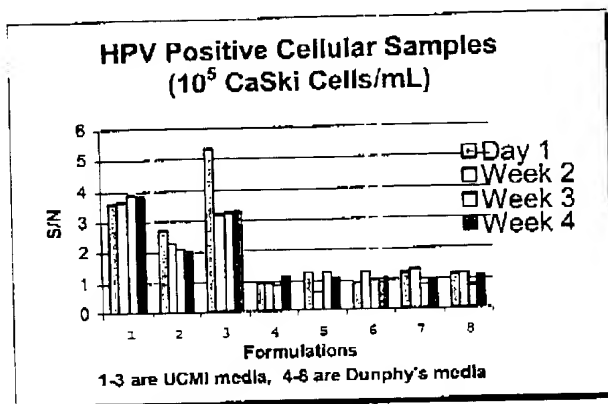


Figure 2(C) shows the results of the Signal to Noise (S/N) values (y-axis) of the HPV positive samples (10^5 CaSki cells/mL) in each of the eight formulations, where the Hybrid Capture II HPV RNA assays were performed at each of the nucleic acid study time points.

FIGURE 2(D):

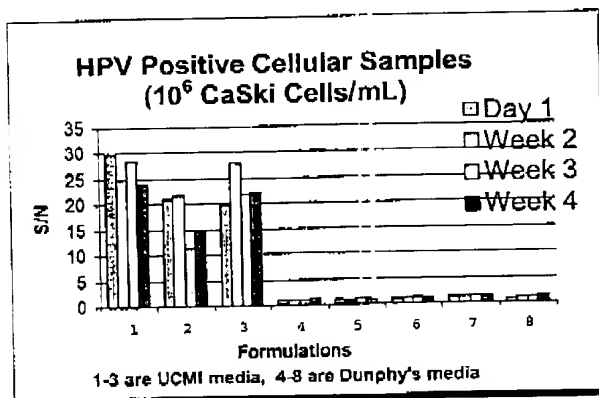


Figure 2(D) shows the results of the Signal to Noise (S/N) values (y-axis) of the HPV positive samples (10^6 CaSki cells/mL) in each of the eight formulations, where the Hybrid Capture II HPV RNA assays were performed at each of the nucleic acid study time points.

22. The UCM data from the RNA stability assays provide the following results: The positive control HPV16 RNA spiked into these three formulations gave significantly different results. Only Formulation No. 2, which lacks the cross linking agent (GSB), gave a robust and consistent signal over the course of the study (Tables 3

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and 4; Figures 2A-2D). Formulation Nos. 1 and 3 had a weak signal at Day 1 that decreased dramatically over time, indicating that *in vitro* transcribed RNA is not stable in the UCM I formulations that utilize GSB. The negative control performed as expected in these formulations. The HPV positive cellular samples gave consistent signals for these three formulations over time. In general, the samples in Formulation No. 2, where the cross linking reagent was omitted gave lower signals than either Formulation No. 1 or 3. The cross linking agent may help reduce RNase activity and/or stabilize cellular RNA in the cellular samples. The chelating agent, EDTA, is not known to efficiently inhibit RNase activity, therefore the addition of EDTA does not stabilize RNA and no significant decrease was observed between Formulation Nos. 1 and 3.

23. The Dunphy data from the RNA stability assays provide the following results: Dunphy's media are not suitable for nucleic acid storage because they failed in every formulation and at every time point to preserve RNA (Tables 3, 4 and Figure 2). The addition of EDTA to Dunphy's Formulation Nos. 5, 6, or 8 had no effect on the stability of nucleic. Neutralizing the pH of the Dunphy's media (Formulation Nos. 7 and 8) also failed to stabilize the cellular RNA.

24. Thus, all tested compositions based on Dunphy's Example 4 formulation for tissue preservation failed to preserve the HPV DNA or RNA properly, as compared to applicants' UCM formulations. Formulations 4-8 of Tables 2 and 4 and Figures 1 and 2 show that the Dunphy-based compositions are not able to preserve the integrity of cellular DNA or RNA, as the S/N ratios are below 2. In contrast, as

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reported in the instant application, the UCM composition properly preserves both the cellular DNA and RNA for hybrid capture assays. The preservation capability of the UCM formulation is apparent as the signal to noise ratio was strongly positive for both DNA and RNA analysis.

25. In contrast to Dunphy's teachings that PEG with a molecular weight between 7000 and 8000 is preferred for stabilizing cellular samples, these experiments demonstrate that glutaraldehyde may be effectively used as a fixative in Digene's UCM formulations. EDTA is a chelating agent that may reduce DNase activity. These experiments have demonstrated that the addition of EDTA in Digene's UCM formulations does help to stabilize cellular DNA that is stored at room temperature over a period of four weeks. However, the addition of EDTA to Dunphy's formulations does not stabilize the nucleic acids, as determined by little detectable signal from the HPV positive samples.

26. Since DNA is known to be unstable when stored for longer periods of time in an acidic environment (JJ Green, Rao VB. Recombinant DNA Principles and Methodologies. Marcel Dekker, USA 1998, p. 23), Dunphy's formulations were neutralized to determine if neutralizing the pH would stabilize the nucleic acids. However, nucleic acids stored in any of the Dunphy's media could not be detected.

27. These experiments demonstrate that Dunphy's media is not suitable for the storage of nucleic acids, in any variation. Digene's UCM formulations are suitable.

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28. I declare further that all statements made on information and belief are believed to be true, and, further, that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and such willful false statements may jeopardize the validity of the instant patent specification or any patent issuing thereon.

Respectfully submitted,

Date: March 25, 2003

Attila T. Lörincz
Attila T. Lörincz, Ph.D.

Curriculum Vitae

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University Education:

Graduate, 1976-1979 Department of Genetics, Trinity College, Dublin, Ireland.
Ph.D., 1980. Research project: Investigation of cell size and cell division control in *Saccharomyces cerevisiae*.

Undergraduate, 1972-1976 University College, Dublin, Ireland.
B.Sc., Honors 1976. Microbiology (major), Biochemistry (minor).
Research project: Characterization of an α -amylase of *Pseudomonas saccharophila*.

Professional Positions:

Senior Vice President and Chief Scientific Officer, since 2000, Digene Corporation, Gaithersburg, Maryland 20878.
Report directly to company President and CEO. Responsibilities include: key role in company policy decision-making at the executive committee level; speaking at scientific meetings worldwide as an acknowledged expert on human papillomaviruses and genetic testing; instigating and supervising basic scientific research; collaborating with scientists worldwide in studies published in prestigious peer-reviewed journals; evaluating Digene's position on intellectual property; evaluating new technology in other laboratories for possible licensing or other use by Digene; representing Digene and its technology at business meetings worldwide.

Vice President, R&D, and Scientific Director, 1990-1999.
Responsibilities included: supervision and guidance of up to 40 scientists, long-range scientific planning for the company, review of detailed research plans, assurance of quality results, and timely achievement of company R&D goals. Principal areas of research focus were the development of diagnostic nucleic acid probe tests for a broad range of human infectious diseases, cancers, and inherited disorders. Other responsibilities included the planning and coordination of clinical studies, U.S. Food and Drug Administration submissions, and interactions with high-level biomedical consultants and collaborators from universities and other companies.

Lecturer, 1999. Zanvyl Krieger School of Arts and Sciences, Johns Hopkins University, Montgomery County Center, Rockville, MD 20850.
Designed and taught a new course in the history of medical diagnostics for candidates for the M.A. in Biotechnology.

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Adjunct Associate Professor, 1989-present. Department of Pathology, Georgetown University Medical School, Washington, DC 20007.

Research efforts focused on human papillomaviruses, with particular emphasis on diagnostic applications, and on molecular mechanisms of carcinogenesis in human keratinocytes. Other projects involved the study of tumor suppressor genes and their use as markers for cancer prognosis.

Scientific Director, Corporate Research, 1989-1990. Life Technologies, Inc., Gaithersburg, Maryland. Studied *in vitro* transcription, transgenic animals, and other model systems of interest to research scientists for the purpose of generating research reagents.

Section Head of Advanced Molecular Diagnostics, 1984-1989. Life Technologies, Inc. Gaithersburg, Maryland. Investigated medical and molecular aspects of the human papillomavirus.

Research Scientist, 1982-1984. University of California at Santa Barbara. Investigated regulation and organization of *S. cerevisiae* genes involved in cell cycle control.

Research Scientist, 1980-1982. University of California at San Diego. Performed quantitative computer analyses of protein regulation during the cell cycle of *S. cerevisiae*, using two-dimensional gel electrophoresis.

Honors And Other Professional Activities:

High Technology Council of Maryland Award for Biotechnology Product of the Year 2000, awarded to the Hybrid Capture® II HPV DNA Test.

American Venereal Disease Association A.V.D.A. Achievement Award 1994, presented in recognition of outstanding contributions toward the control of sexually transmitted diseases.

Primary author of cell cycle paper in Nature, 1984.

Senior author of papers in JAMA, 2000, detailing the role of HPV in cervical cancer screening.

Editorial board member of IVD Technology and of Clinical and Diagnostic Virology.

Scientific and medical reviewer for: Obstetrics and Gynecology, Science, Journal of Clinical Microbiology, Journal of General Virology, Clinical and Diagnostic Virology, and others.

Peer reviewer for the National Institutes of Health, since 1986.

Life Technologies, Inc., David L. Coffin Award for Technical Innovation, for developing the FDA approved HPV test ViraPap®, 1989.

Life Technologies, Inc., David L. Coffin Patent Award, for human papillomavirus 56 nucleic acid hybridization probes and methods for employing same, US Patent No. 4,908,306.

Irish Department of Education Ph.D. Scholarship Recipient, 1976-1979.

National Clinical Trials:

Co-principal investigator for HPV QC Group in the NCI ALTS study to investigate alternatives in women's health care for managing cervical disease. Contract NCI-CN-55044-07, awarded 1995.

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Federal Research Grants:

Principal Investigator for Contract N44-AI-85335, "Rapid Detection and Typing of HSV DNA." SBIR Phase II grant from NIAID, awarded May, 1998.

Principal Investigator for Contract N43-AI-45214, "Rapid Detection and Typing of Herpes Simplex virus (HSV) DNA in Clinical Specimens." SBIR Phase I grant from NIAID, completed 1996.

Subcontract MA-5623-26 with Microbiological Associates, Inc., "Assays to Detect and Type Human Papillomavirus DNA in Cervical Lavage Samples." Completed 1995.

Patents:

US patent nos. 4,849,331; 4,849,332; 4,849,334; and 4,908,306 for the use of HPV types 35, 43, 44, and 56 in diagnostic testing.

US patent nos. 5,981,179 and 6,027,897 and Australian patent no. 711130 for CAR target amplification technology.

Australian patent no. 673813 for Hybrid Capture[®] technology.

Other patents pending for Hybrid Capture[®] technology.

Memberships:

American Society for Microbiology (since 1980)

Pan American Group for Rapid Viral Diagnosis (since 1986)

American Association of Clinical Chemistry (since 1991)

International Committee on HPV Nomenclature (1986-1991)

International Conferences

Dr. Lőrincz has been an invited speaker at many international conferences, a list of which is available on request.

Departmental Seminars

Dr. Lőrincz has been an invited speaker at many departmental seminars, a list of which is available on request.

Managerial Experience:

- Head of several scientific teams, with full responsibilities for project planning, budgets, hiring, promotions, data analyses, presentations, publications, etc. Principal investigator for numerous clinical studies. As a member of the executive staff of Digene, I am intimately involved in setting overall company objectives and policies.
- Head of several multi-disciplinary strategic planning teams involving R&D, Regulatory Affairs, Marketing and Sales, Development, and Manufacturing.
- Director of Intellectual Property for Digene Corporation, 1990-1994. Prepared patent applications with assistance of attorneys.

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- Played a major role in preparing several PMA applications for Life Technologies' and Digene's HPV testing kits. Presented data to FDA panels, leading to successful approval of the ViraType® and Hybrid Capture® kits for detecting and typing HPV DNA.
- Key member of the Executive Committee directing a successful initial public offering of Digene Corporation on NASDAQ in May, 1996, and a secondary offering in October, 1997.

SELECTED PUBLICATIONS

Dr. Lőrincz has 72 peer-reviewed scientific publications prior to 1995, a list of which is available on request. A list of peer-reviewed publication since 1995 follows:

- Schiffman, M.H., N.B. Kiviat, R.D. Burk, K.V. Shah, R.W. Daniel, R. Lewis, J. Kuypers, M.M. Manos, D.R. Scott, M.E. Sherman, R.J. Kurman, M.H. Stoler, A.G. Glass, B.B. Rush, I. Mielzynska, and A.T. Lorincz (1995) Accuracy and interlaboratory reliability of human papillomavirus DNA testing by Hybrid Capture. *J. Clin. Microbiol.* 33:545-550.
- Cox, J.T., A.T. Lorincz, M.H. Schiffman, M.E. Sherman, A. Cullen, and R.J. Kurman (1995) Human papillomavirus testing by hybrid capture appears to be useful in triaging women with a cytologic diagnosis of atypical squamous cells of undetermined significance. *Am. J. Obstet. Gynecol.* 172(3):946-954.
- Reid, R., and A.T. Lőrincz (1995) Human papillomavirus tests. In: Ballière's Clinical Obstetrics and Gynaecology (H.W. Jones, III, guest ed.), vol. 9, no. 1, pp. 63-103. Ballière Tindall, London.
- Lorincz, A. (1995) Hybrid Capture™: A simple, sensitive method for the routine detection of HPV DNA. In: Screening of Cervical Cancer: For Whom, Why and How? Experts' Conference. 2nd International Congress of Papillomavirus in Human Pathology. Paris, France, Unesco, April 6, 7, 8, 1994 (Monsonogo, J., ed.), pp. 59-62. EUROGIN Scientific Publications, Paris.
- Wideroff, L.; Schiffman, M.H.; Nonnenmacher, B.; Hubbert, N.; Kimbauer, R.; Greer, C.E.; Lowy, D.; Lorincz, A.T.; Manos, M.M.; Glass, A.G.; Scott, D.R.; Sherman, M.E.; Kurman, R.J.; Buckland, J.; Tarone, R.E.; Schiller, J. (1995) Evaluation of seroreactivity to human papillomavirus type 16 virus-like particles in an incident case-control study of cervical neoplasia. *J. Infect. Dis.* 172(6):1425-1430.
- Lőrincz, A. (1995) Human papillomaviruses. In: Diagnostic Procedures for Viral, Rickettsial, and Chlamydial Infections, 7th edition (Lennette, E.H., et al., eds.), pp. 465-480. American Public Health Association, Washington, D.C.
- Lőrincz, A. (1996) Hybrid Capture™ method for detection of human papillomavirus DNA in clinical specimens. *Papillomavirus Report* 7(1):1-7.
- Reid, R.; Lőrincz, A. (1996) New generation of human papillomavirus tests. In: Cervical Cancer and Preinvasive Neoplasia (Rubin, S.C.; Hoskins, W.J., eds.), pp. 27-47. Lippincott-Raven, Philadelphia.
- Lőrincz, A.T. (1996) Molecular methods for the detection of human papillomavirus infection. In: Obstetrics and Gynecology Clinics of North America: The Papillomaviruses, 2nd edition (Lőrincz, A.T.; Reid, R., eds.), vol. 23, no. 3, pp. 707-730. W.B. Saunders, Philadelphia.
- Tsukui, T.; Hildesheim, A.; Schiffman, M.H.; Lucci, J., III; Contois, D.; Lawler, P.; Rush, B.B.; Lorincz, A.T.; Corrigan, A.; Burk, R.D.; Qu, W.; Marshall, M.A.; Mann, D.; Carrington, M.; Clerici, M.; Shearer, G.M.; Carbone, D.P.; Scott, D.R.; Houghten, R.A.; Berzofsky, J.A. (1996) Interleukin 2 production *in vitro* by peripheral lymphocytes in response to human papillomavirus-derived peptides: correlation with cervical pathology. *Cancer Res.* 56(17):3967-3974.
- Hall, S.; Lőrincz, A.; Shah, F.; Sherman, M.E.; Abbas, F.; Paull, G.; Kurman, R.J.; Shah, K.V. (1996) Human papillomavirus DNA detection in cervical specimens by Hybrid Capture: correlation with cytologic and histologic diagnoses of squamous intraepithelial lesions of the cervix. *Gynecol. Oncol.* 62:353-359.
- Wideroff, L.; Schiffman, M.H.; Hoover, R.; Tarone, R.E.; Nonnenmacher, B.; Hubbert, N.; Kimbauer, R.; Greer, C.E.; Lorincz, A.T.; Manos, M.M.; Glass, A.G.; Scott, D.R.; Sherman, M.E.; Buckland, J.; Lowy, D.; Schiller, J. (1996) Epidemiologic determinants of seroreactivity to human papillomavirus (HPV) type 16 virus-like particles in cervical HPV-16 DNA-positive and -negative women. *J. Infect. Dis.* 174(5):937-943.

- Lőrincz, A.T. (1996) Hybrid Capture™ method for detection of human papillomavirus DNA in clinical specimens: a tool for clinical management of equivocal Pap smears and for population screening. *J. Obstet. Gynaecol. Res.* 22(6):629-636.
- Lőrincz, A. (1997) Human papillomavirus testing. *Pathology Case Reviews* 2(1):43-48.
- Sherman, M.E.; Schiffman, M.H.; Lőrincz, A.T.; Herrero, R.; Hutchinson, M.; Bratti, C.; Zahniser, D.; Morales, J.; Hildesheim, A.; Helgesen, K.; Kelly, D.; Alfaro, M.; Mena, F.; Balmaceda, I.; Mango, L.; Greenberg, M. (1997) Cervical specimens collected in liquid buffer are suitable for both cytologic screening and ancillary human papillomavirus testing. *Cancer* 81(2):89-97.
- Sherman, M.E.; Schiffman, M.H.; Mango, L.J.; Kelly, D.; Acosta, D.; Cason, Z.; Elgert, P.; Zaleski, S.; Scott, D.R.; Kurman, R.J.; Kiviat, N.B.; Stoler, M.; Lorincz, A.T. (1997) Evaluation of PAPNET testing as an ancillary tool to clarify the status of the "atypical" cervical smear. *Mod. Pathol.* 10(6):564-571.
- Cope, J.U.; Hildesheim, A.; Schiffman, M.H.; Manos, M.M.; Lőrincz, A.T.; Burk, R.D.; Glass, A.G.; Greer, C.; Buckland, J.; Helgesen, K.; Scott, D.R.; Sherman, M.E.; Kurman, R.J.; Liaw, K.-L. (1997) Comparison of the Hybrid Capture tube test and PCR for detection of human papillomavirus DNA in cervical specimens. *J. Clin. Microbiol.* 35(9):2262-2265.
- Cullen, A.P.; Long, C.D.; Lőrincz, A.T. (1997) Rapid detection and typing of herpes simplex virus DNA in clinical specimens by the Hybrid Capture II signal amplification probe test. *J. Clin. Microbiol.* 35(9):2275-2278.
- Lőrincz, A.T. (1997) Methods of DNA hybridization and their clinical applicability to human papillomavirus detection. In: *New Developments in Cervical Cancer Screening and Prevention* (Franco, E.; Monsonego, J., eds.), pp. 325-337. Blackwell Science, Oxford.
- Herrero, R.; Schiffman, M.H.; Bratti, C.; Hildesheim, A.; Sherman, M.E.; Morales, J.; Mekbel, S.; Alfaro, M.; Balmaceda, I.; Greenberg, M.; Lorincz, A. (1997) Evaluation of multiple screening techniques in a high-risk area: the Guanacaste project. In: *New Developments in Cervical Cancer Screening and Prevention* (Franco, E.; Monsonego, J., eds.), pp. 389-399. Blackwell Science, Oxford.
- Chesebro, M.J.; Everett, W.D.; Lőrincz, A. (1997) High-risk human papillomavirus testing of women with cytological low-grade squamous intraepithelial lesions. *J. Lower Genital Tract Dis.* 1(4):234-239.
- Hildesheim, A.; Schiffman, M.H.; Tsukui, T.; Swanson, C.A.; Lucci, J., III; Scott, D.R.; Glass, A.G.; Rush, B.B.; Lorincz, A.T.; Corigan, A.; Burk, R.D.; Helgesen, K.; Houghten, R.A.; Sherman, M.E.; Kurman, R.J.; Berzofsky, J.A.; Kramer, T.R. (1997) Immune activation in cervical neoplasia: cross-sectional association between plasma soluble interleukin 2 receptor levels and disease. *Cancer Epidemiol. Biomarkers Prev.* 6(10):807-813.
- Ferris, D.G.; Wright, T.C., Jr.; Litaker, M.S.; Richart, R.M.; Lorincz, A.T.; Sun, X.-W.; Woodward, L. (1998) Comparison of two tests for detecting carcinogenic HPV in women with Papanicolaou smear reports of ASCUS and LSIL. *J. Fam. Pract.* 46(2):136-141.
- Ferris, D.G.; Wright, T.C., Jr.; Litaker, M.S.; Richart, R.M.; Lorincz, A.T.; Sun, X.-W.; Borgatta, L.; Buck, H.; Kramer, L.; Rubin, R. (1998) Triage of women with ASCUS and LSIL on Pap smear reports: management by repeat Pap smear, HPV DNA testing, or colposcopy? *J. Fam. Pract.* 46(2):125-134.
- Lőrincz, A.T.; Cullen, A.; Long, C. (1998) Rapid detection and typing of herpes simplex virus DNA in clinical specimens by the Hybrid Capture II signal amplification probe test [Authors' reply to letter to the editor]. *J. Clin. Microbiol.* 36(3):852.
- Wright, T.C., Jr.; Lorincz, A.; Ferris, D.G.; Richart, R.M.; Ferenczy, A.; Mielzynska, I.; Borgata, L. (1998) Reflex human papillomavirus DNA testing in women with abnormal Papanicolaou smears. *Am. J. Obstet Gynecol.* 178(5):962-966.
- Lőrincz, A. (1998) Hybrid Capture. *Clin. Chem.* 44(6):1363.
- Nindl, I.; Lőrincz, A.; Mielzynska, I.; Petry, U.; Baur, S.; Kirchmayr, R.; Michels, W.; Schneider, A. (1998) Human papillomavirus detection in cervical intraepithelial neoplasia by a second-generation hybrid capture microplate test, comparing two different cervical specimen collection methods. *Clin. Diagn. Virol.* 10:49-56.

- Lörincz, A.; Davies, P.O. (1998) The Hybrid Capture II Assay for the detection of human papillomavirus. In: Genital Infections and Neoplasia Update. (Monsonago, J., editor), pp 18-19. EUROGIN Scientific Publications, Paris.
- Peyton, C.L.; Schiffman, M.; Lörincz, A.T.; Hunt, W.C.; Mielzynska, I.; Bratti, C.; Eaton, S.; Hildesheim, A.; Morera, L.A.; Rodriguez, A.C.; Herrero, R.; Sherman, M.E.; Wheeler, C.M. (1998) Comparison of PCR- and Hybrid Capture-based human papillomavirus detection systems using multiple cervical specimen collection strategies. J. Clin. Microbiol. 36(11):3248-3254.
- Hildesheim, A.; Schiffman, M.; Scott, D.R.; Marti, D.; Kissner, T.; Sherman, M.E.; Glass, A.G.; Manos, M.M.; Lörincz, A.T.; Kurman, R.J.; Buckland, J.; Rush, B.B.; Carrington, M. (1998) Human leukocyte antigen class I/II alleles and development of human papillomavirus-related cervical neoplasia: results from a case-control study conducted in the United States. Cancer Epidemiol. Biomarkers Prev. 7:1035-1041.
- Sherman, M.E.; Schiffman, M.; Herrero, R.; Kelly, D.; Bratti, C.; Mango, L.; Alfaro, M.; Hutchinson, M.L.; Mena, F.; Hildesheim, A.; Morales, J.; Greenberg, M.; Balmaceda, I.; Lörincz, A.T. (1998) Performance of a semiautomated Papanicolaou smear screening system: results of a population-based study conducted in Guanacaste, Costa Rica. Cancer 84(5):273-280.
- Schneider, D.L.; Herrero, R.; Bratti, C.; Greenberg, M.D.; Hildesheim, A.; Sherman, M.E.; Morales, J.; Hutchinson, M.L.; Sedlacek, T.V.; Lörincz, A.; Mango, L.; Wacholder, S.; Alfaro, M.; Schiffman, M. (1999) Cervicography screening for cervical cancer among 8460 women in a high-risk population. Am. J. Obstet. Gynecol. 180(2):290-298.
- Greenberg, M.D.; Reid, R.; Schiffman, M.; Campion, M.J.; Precop, S.L.; Berman, N.R.; Zemlo, T.; Husain, M.; Herman, G.; Omato, K.H.; Lörincz, A.T. (1999) A prospective study of biopsy-confirmed cervical intraepithelial neoplasia grade 1: colposcopic, cytologic, and virologic risk factors for progression. J. Lower Gen. Tract Dis. 3(2):104-110.
- Girdner, J.L.; Cullen, A.P.; Salama, T.G.; He, L.; Lörincz, A.; Quinn, T.C. (1999) Evaluation of the Digene Hybrid Capture II CT-ID test for the detection of *Chlamydia trachomatis* in female endocervical specimens. J. Clin. Microbiol. 37(5):1579-1581.
- Cox, J.T.; Herbst, A.L.; Kinney, W.; Lörincz, A.T.; Richart, R.M.; Schiffman, M.H. (1999) Advanced technologies in cervical cancer screening: ASCCP biennial meeting 1998. J. Lower Gen. Tract Dis. 3(suppl 1):S8-S28.
- Modarress, K.J.; Cullen, A.P.; Jaffurs, W.J., Sr.; Troutman, G.L.; Mousavi, N.; Hubbard, R.A.; Henderson, S.; Lörincz, A.T. (1999) Detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in swab specimens by the Hybrid Capture II and PACE 2 nucleic acid probe tests. Sex. Transm. Dis. 26(5):303-308.
- Hutchinson, M.L.; Zahriser, D.J.; Sherman, M.E.; Herrero, R.; Alfaro, M.; Bratti, M.C.; Hildesheim, A.; Lörincz, A.T.; Greenberg, M.D.; Morales, J.; Schiffman, M. (1999) Utility of liquid-based cytology for cervical carcinoma screening: results of a population-based study conducted in a region of Costa Rica with a high incidence of cervical carcinoma. Cancer Cytopathol. 87(2):48-55.
- Lörincz, A.T. (1999) Human papillomaviruses. In: Lennette E.H., Smith T.F., editors. Laboratory Diagnosis of Viral Infections. 3rd ed. New York: Marcel Dekker; pp. 635-663.
- Harper, D.M.; Hildesheim, A.; Cobb, J.L.; Greenberg, M.; Vaught, J.; Lörincz, A.T. (1999) Collection devices for human papillomavirus. J. Fam. Pract. 48(7):531-535.
- Cuzick, J.; Beverley, E.; Ho, L.; Terry, G.; Sapper, H.; Mielzynska, I.; Lörincz, A.; Chan, W.-K.; Krausz, T.; Soutter, P. (1999) HPV testing in primary screening of older women. Br. J. Cancer 81(3):554-558.
- Serwadda, D.; Wawer, M.J.; Shah, K.V.; Sewankambo, N.K.; Daniel, R.; Li, C.; Lörincz, A.; Meehan, M.P.; Wabwire-Mangen, F.; Gray, R.H. (1999) Use of a Hybrid Capture assay of self-collected vaginal swabs in rural Uganda for detection of human papillomavirus. J. Infect. Dis. 180(4):1316-1319.
- Lazar, J.G.; Cullen, A.P.; Mielzynska, I.; Meijide, M.G.; Lörincz, A.T. (1999) Hybrid Capture®: a sensitive signal amplification-based chemiluminescent test for the detection and quantitation of human viral and bacterial pathogens. J. Clin. Ligand Assay, 22(2):139-151.
- Schachter, J.; Hook, E.W., III; McCormack, W.M.; Quinn, T.C.; Chernesky, M.; Chong, S.; Girdner, J.L.; Dixon, P.B.; DeMeo, L.; Williams, E.; Cullen, A.; Lörincz, A. (1999) Ability of the Digene Hybrid Capture II

test to identify *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in cervical specimens. *J. Clin. Microbiol.* 37(11):3668-3671.

Wright, T.C., Jr.; Denny, L.; Kuhn, L.; Pollack, A.; Lorincz, A. (2000) HPV DNA testing of self-collected vaginal samples compared with cytologic screening to detect cervical cancer. *JAMA* 283(1):81-86.

Schiffman, M.; Herrero, R.; Hildesheim, A.; Sherman, M.E.; Bratti, M.; Wacholder, S.; Alfaro, M.; Hutchinson, M.; Morales, J.; Greenberg, M.D.; Lorincz, A.T. (2000) HPV DNA testing in cervical cancer screening: results from women in a high-risk province of Costa Rica. *JAMA* 283(1):87-93.

Kuhn, L.; Denny, L.; Pollack, A.; Lorincz, A.; Richart, R.M.; Wright, T.C. (2000) Human papillomavirus DNA testing for cervical cancer screening in low-resource settings. *J. Natl. Cancer Inst.* 92(10):818-825.

Liaw, K.-L.; Schiffman, M.; Cope, J.U.; Glass, A.G.; Manos, M.M.; Sherman, M.E.; Burk, R.D.; Hildesheim, A.; Lorincz, A.T. (2000) Update on recent clinical studies using HPV testing for screening and diagnosis of cervical neoplasia. *CME J. Gynecol. Oncol.* 5(1):41-44.

Denny, L.; Kuhn, L.; Risi, L.; Richart, R.M.; Pollack, A.; Lorincz, A.; Kostecki, F.; Wright, T.C., Jr. (2000) Two-stage cervical cancer screening: An alternative for resource-poor settings. *Am. J. Obstet. Gynecol.* 183(2):383-388.

Anthony, J.G.; Linske-O'Connell, L.; Lorincz, A.T. (2000) Nucleic acid hybridization. In: Specter, S.; Hodinka, R.L.; Young, S.A., editors. *Clinical Virology Manual*. 3rd ed. Washington, DC: ASM Press, pp. 169-81.

Sellers, J.W.; Mahony, J.B.; Kaczorowski, J.; Lytwyn, A.; Bangura, H.; Chong, S.; Lorincz, A.; Dalby, D.M.; Janjusevic, V.; Keller, J.L.; for the Survey of HPV in Ontario Women (SHOW) Group. (2000) Prevalence and predictors of human papillomavirus infection in women in Ontario, Canada. *Canadian Medical Association Journal* 163(5):503-508.

Sellers, J.W.; Lorincz, A.T.; Mahony, J.B.; Mielzynska, I.; Lytwyn, A.; Roth, P.; Howard, M.; Chong, S.; Daya, D.; Chapman, W.; Chernesky, M. (2000) Comparison of self-collected vaginal, vulvar and urine samples for human papillomavirus testing to detect high-grade squamous intraepithelial lesions. *Canadian Medical Association Journal* 163(5):513-518.

Lytwyn, A.; Sellers, J.W.; Mahony, J.B.; Daya, D.; Chapman, W.; Ellis, N.; Roth, P.; Lorincz, A.T.; Gafni, A.; for the HPV Effectiveness in Lowgrade Paps (HELP) Study No. 1 Group. (2000) Comparison of human papillomavirus DNA testing and repeat Papanicolaou test in women with low-grade cervical cytologic abnormalities: a randomized trial. *Canadian Medical Association Journal* 163(6):701-707.

Bozzetti, M.; Nonnenmacher, B.; Mielzynska, I.; Villa, L.; Lorincz, A.; Breitenbach, V.; Prolla, J. (2000) Comparison between hybrid capture II and polymerase chain reaction results among women at low risk for cervical cancer. *Ann. Epidemiol.* 10(7):466.

Belinson, J.; Qiao, Y.; Pretorius, R.; Keaton, K.; Elson, P.; Fischer, C.; Lorincz, A.; Zahniser, D.; Wilbur, D.; Pan, Q.; Li, L.; Zhang, W.; Lee, A.; Wu, L.; Ling, Y. Prevalence of cervical cancer and feasibility of screening in rural China: a pilot study for the Shanxi Province Cervical Cancer Screening Study. Manuscript completed.

Pretorius, R.G.; Peterson, P.; Novak, S.; Azizi, F.; Sadeghi, M.; Lorincz, A.T. Comparison of the first and second generation Hybrid Capture tests for high-risk human papillomavirus as an aid to colposcopy. Manuscript completed.

Attachment A

PUBLICATIONS, 1977-1994

- Jagdish, M.N., A.T. Lőrincz, and B.L.A. Carter (1977) Cell size and cell division in yeast cultured at different growth rates. *FEMS Microbiol. Lett.* 2:235-237.
- Carter, B.L.A., A.T. Lőrincz, and G.C. Johnston (1978) Protein synthesis, cell division and the cell cycle in *Saccharomyces cerevisiae* following a shift to a richer medium. *J. Gen. Microbiol.* 106:222-225.
- Johnston, G.C., C.W. Ehrhardt, A.T. Lőrincz, and B.L.A. Carter (1979) Regulation of cell size in the yeast *Saccharomyces cerevisiae*. *J. Bacteriol.* 137:1-5.
- Lőrincz, A.T. and B.L.A. Carter (1979) Control of cell size at bud initiation in *Saccharomyces cerevisiae*. *J. Gen. Microbiol.* 113:287-295.
- Lőrincz, A.T., M.J. Miller, N.-H. Xuong, and E.P. Geiduschek (1982) Identification of proteins whose synthesis is modulated during the cell cycle of *Saccharomyces cerevisiae*. *Mol. Cell. Biol.* 2:1532-1549.
- Lőrincz, A.T. and B.L.A. Carter (1983) Cell cycle initiation and bud emergence in *Saccharomyces cerevisiae*. *J. Gen. Microbiol.* 129:1599-1605.
- Lőrincz, A.T. and S.I. Reed (1984) Primary structure homology between the product of yeast cell division control gene *CDC 28* and vertebrate oncogenes. *Nature* 307:183-185.
- Reed, S.I., J.A. Hadwiger and A.T. Lőrincz, (1985) Protein kinase activity associated with the product of the yeast cell division cycle gene *CDC 28*. *Proc. Natl. Acad. Sci. USA* 82:4055-4059.
- Reed, S.I., M.A. deBarros Lopes, J. Ferguson, J.A. Hadwiger, J.-Y. Ho, R. Horwitz, C.A. Jones, A.T. Lőrincz, M.D. Mendenhall, T.A. Peterson, S. Richardson, and C. Wittenburg (1985) Genetic and molecular analysis of division control in yeast. *Cold Spring Harb. Symp. Quant. Biol.* 50:627-634.
- Lőrincz, A.T. and S.I. Reed (1986) Sequence analysis of temperature-sensitive mutations in the *Saccharomyces cerevisiae* gene *CDC 28*. *Mol. Cell. Biol.* 6:4099-4103.
- Lőrincz, A.T., W.D. Lancaster, and G.F. Temple (1986) Cloning and characterization of the DNA of a new human papillomavirus from a woman with dysplasia of the uterine cervix. *J. Virol.* 58:225-229.
- Lőrincz, A.T., W.D. Lancaster, R.J. Kurman, A.B. Jenson, and G.F. Temple (1986) Characterization of human papillomaviruses in cervical neoplasias and their detection in routine clinical screening. In: *Banbury Report 21: Viral Etiology of Cervical Cancer* (T. Peto and H. zur Hausen, eds.), pp. 225-237. Cold Spring Harbor Laboratory, New York.
- Lőrincz, A.T., G.F. Temple, J.A. Patterson, A.B. Jenson, R.J. Kurman, and W.D. Lancaster (1986) Correlation of cellular atypia and human papillomavirus deoxyribonucleic acid sequences in exfoliated cells of the uterine cervix. *Obstet. Gynecol.* 68:508-512.
- Reid, R., M. Greenberg, A.B. Jenson, M. Husain, J. Willett, Y. Daoud, G. Temple, C.R. Stanhope, A.I. Sherman, G.D. Phibbs, and A.T. Lőrincz (1987) Sexually transmitted papillomaviral infections. I. The anatomic distribution and pathologic grade of neoplastic lesions associated with different viral types. *Am. J. Obstet. Gynecol.* 156:212-222.
- Lőrincz, A.T., A.P. Quinn, W.D. Lancaster, and G.F. Temple (1987) A new type of papillomavirus associated with cancer of the uterine cervix. *Virology* 159:187-190.
- Lőrincz, A.T. (1987) Detection of human papillomavirus infection by nucleic acid hybridization. In: *Obstetrics and Gynecology Clinics of North America* (Reid, R., ed.), vol. 14, pp. 451-469. W.B. Saunders, Philadelphia.
- Lőrincz, A.T., G.F. Temple, R.J. Kurman, A.B. Jenson, and W.D. Lancaster (1987) Oncogenic association of specific human papillomavirus types with cervical neoplasia. *J. Natl. Canc. Inst.* 79:671-677.
- Naghashfar, Z.S., N.B. Rosenshein, A.T. Lőrincz, J. Buscema, and K.V. Shah (1987) Characterization of human papillomavirus type 45, a new type 18-related virus of the genital tract. *J. Gen. Virol.* 68:3073-3079

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- Barnes, W., G. Delgado, R.J. Kurman, E.S. Pettrilli, D.M. Smith, S. Ahmed, A.T. Lörincz, G.F. Temple, A.B. Jenson, and W.D. Lancaster (1988) Possible prognostic significance of human papillomavirus type in cervical cancer. *Gynecol. Oncol.* 29:267-273.
- Kurman R.J., M.H. Schiffman, W.D. Lancaster, R. Reid, A.B. Jenson, G.F. Temple and A.T. Lörincz (1988) Analysis of individual human papillomavirus types in cervical neoplasia. A possible role for type 18 in rapid progression. *Am. J. Obstet. Gynecol.* 159:293-296.
- Shimoda K., A.T. Lörincz, G.F. Temple, and W.D. Lancaster (1988) Human papillomavirus type 52: a new virus associated with cervical neoplasia. *J. Gen. Virol.* 69:2925-2928.
- Rosemberg, S.K., R. Reid, M. Greenberg, and A.T. Lörincz (1988) Sexually transmitted papillomaviral infection in the male: the urethral reservoir. *Urology* 32:47-49.
- Schachter, J., J. Moncada, C.R. Dawson, S. Sheppard, P. Courtright, M.E. Said, S. Zaki, S.F. Hafez, and A.T. Lörincz (1988) Nonculture methods for diagnosing chlamydial infection in patients with trachoma: a clue to the pathogenesis of the disease. *J. Infect. Dis.* 158:1347-1352.
- Willett, G.D., R.J. Kurman, R. Reid, M. Greenberg, A.B. Jenson, and A.T. Lörincz (1989) Correlation of the histologic appearance of intraepithelial neoplasia of the cervix with human papillomavirus types: emphasis on low grade lesions including so-called flat condyloma. *Int. J. Gynecol. Pathol.* 8:18-25.
- Lörincz, A.T., A.P. Quinn, M.D. Goldsborough, B.J. Schmidt, and G.F. Temple (1989) Cloning and partial DNA sequencing of two new human papillomavirus types associated with condylomas and low-grade cervical neoplasia. *J. Virol.* 63:2829-2834.
- Goldsborough, M.D., D. DiSilvestre, G.F. Temple, and A.T. Lörincz (1989) Nucleotide sequence of human papillomavirus type 31: a cervical neoplasia-associated virus. *Virol.* 171:306-311.
- Lörincz, A.T., A.P. Quinn, M.D. Goldsborough, P. McAllister, and G.F. Temple (1989) Human papillomavirus type 56: a new virus detected in cervical cancers. *J. Gen. Virol.* 70:3099-3104.
- Lörincz, A.T. and R. Reid (1989) The association of human papillomavirus with gynecologic cancer. *Curr. Opinion Oncol.* 1:123-132.
- Lörincz, A.T. (1989) Human papillomavirus testing. *Diag. Clin. Test.* 27:28-37.
- Lörincz, A.T. (1990) Human papillomavirus detection tests. In: *Sexually Transmitted Diseases*, 2nd edition (Holmes, K.K., et al., eds.), pp. 953-959. McGraw-Hill, New York.
- Lörincz, A.T., M.H. Schiffman, W.J. Jaffurs, J. Marlow, A.P. Quinn, and G.F. Temple (1990) Temporal associations of human papillomavirus infection with cervical cytological abnormalities. *Am. J. Obstet. Gynecol.* 162:645-651.
- Reid, R., M.D. Greenberg, A.T. Lörincz, Y. Daoud, D. Pizzuti, and M. Stoler (1990) Superficial laser vulvectomy. IV. Extended laser vaporization and adjunctive 5-fluorouracil therapy of human papillomavirus associated vulvar disease. *Obstet. Gynecol.* 76:439-448.
- Cullen, A.P., R. Reid, M. Campion, and A.T. Lörincz (1991) Analysis of the physical state of different human papillomavirus DNAs in preinvasive and invasive cervical neoplasms. *J. Virol.* 65:606-612.
- Schiffman, M.H., H.M. Bauer, A.T. Lörincz, M.M. Manos, J.C. Byrne, A.G. Glass, D.M. Cadell, and P.M. Howley (1991) Comparison of Southern blot hybridization and polymerase chain reaction methods for detection of human papillomavirus DNA. *J. Clin. Microbiol.* 29:573-577.
- Reid, R., M.D. Greenberg, A.T. Lörincz, A.B. Jenson, C.R. Lavery, M.D. Husain, Y. Daoud, B. Zado, T. White, D. Cantor, and M. Goldrath (1991) Should cervical cytologic testing be augmented by cervicography or human papillomavirus deoxyribonucleic acid detection? *Am. J. Obstet. Gynecol.* 164:1461-1471.
- Reid, R. and A.T. Lörincz (1991) Should family physicians test for human papillomavirus infection? An affirmative view. *J. Fam. Pract.* 32:1-10.
- Nasser, M., J.R. Gage, A. Lörincz, and F.O. Wettstein (1991) Human papillomavirus type 16 immortalized cervical keratinocytes contain transcripts encoding E6, E7, and E2 initiated at the p97 promoter and express high levels of E7. *Virology* 184:131-140.

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- Lörincz, A (1991) Detection of sexually transmitted pathogens with nucleic acid techniques. Ups. J. Med. Sci. Suppl. 50:39-41.
- Lörincz, A.T., R. Reid, A.B. Jenson, M.D. Greenberg, W.D. Lancaster, and R.J. Kurman (1992) Human papillomavirus infection of the cervix: relative risk associations of 15 common anogenital types. Obstet. Gynecol. 79:328-337.
- Chapman, W.B., A.T. Lörincz, G.D. Willett, V.C. Wright, and R.J. Kurman (1992) Epidermal growth factor receptor expression and the presence of human papillomavirus in cervical squamous intraepithelial lesions. Int. J. Gynecol. Pathol. 11:221-226.
- Kiviat, N.B., L.A. Koutsky, C.W. Critchlow, A.T. Lörincz, A.P. Cullen, J. Brockway and K.K. Holmes (1992) Prevalence and cytologic manifestations of human papillomavirus (HPV) types 6, 11, 16, 18, 31, 33, 35, 42, 43, 44, 45, 51, 52 and 56 among 500 consecutive women. Int. J. Gynecol. Pathol. 11:197-203.
- Lörincz, A (1992) Nucleic acid hybridization. In: Clinical Virology Manual, 2nd edition (Lancz G. and S. Specter, eds.), pp. 285-298. Elsevier, New York.
- Lörincz A (1992) Detection of human papillomavirus DNA without amplification: prospects for clinical utility. In: IARC Scientific Publication No. 119: Human Papilloma Virus and Cervical Cancer (N. Munoz and F.X. Bosch, eds.), pp. 135-145. Oxford University Press, Oxford UK.
- Goldsborough, M.D., P. McAllister, R. Reid, G. Temple, and A.T. Lörincz (1992) A comparison study of human papillomavirus prevalence by the polymerase chain reaction in low risk women and in a gynecology referral group at elevated risk for cervical cancer. Mol. Cell. Probes 6:451-457.
- Munoz, N., F.X. Bosch, S. de Sanjose, L. Tafur, I. Izarzugaza, M. Gili, P. Viladiu, C. Navarro, C. Martos, N. Asuncion, L.C. Gonzalez, J.M. Kaldor, E. Guerrero, A. Lörincz, M. Santamaria, P. Alonso de Ruiz, N. Aristizabal, and K. Shah (1992) The causal link between human papillomavirus and invasive cervical cancer: a population-based case-control study in Columbia and Spain. Int. J. Cancer 52:743-749.
- Lörincz, A (1992) Diagnosis of human papillomavirus infection by the new generation of molecular DNA assays. Clin. Immunol. Newslett. 12:123-128.
- Chapman, W.B., A.T. Lörincz, G.D. Willett, V.C. Wright, and R.J. Kurman (1993) Evaluation of two commercially available *in situ* hybridization kits for detection of human papillomavirus DNA in cervical biopsies: comparison to Southern blot hybridization. Mod. Pathol. 6:73-79.
- Kessis, T.D., R.J. Slebos, W.G. Nelson, M.B. Kastan, B.S. Plunkett, S.M. Han, A.T. Lörincz, L. Hedrick, and K.R. Cho (1993) Human papillomavirus 16 E6 expression disrupts the p53-mediated cellular response to DNA damage. Proc. Natl. Acad. Sci. USA 90:3988-3992.
- Sherman, M.E., M.H. Schiffman, A.T. Lörincz, M.M. Manos, D.R. Scott, R.J. Kurman, N.B. Kiviat, M. Stoler, A.G. Glass, and B.B. Rush (1994) Towards objective quality assurance in cervical cytopathology: correlation of cytopathologic diagnoses with detection of high-risk human papillomavirus types. Am. J. Pathol. 102:182-187.

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Attachment B

INVITED SPEAKER
INTERNATIONAL CONFERENCES

1. Bay Area Yeast Meeting. August 3, 1983. Berkeley, California.
2. Origin of Female Genital Cancer. April 14-17, 1985. Cold Spring Harbor, New York.
3. Workshop on Mechanisms of Transformation by Papillomaviruses. February 18-19, 1986. Bethesda, Maryland.
4. Colposcopy, Cervical and Vulvar Pathology and Gynecologic Laser Surgery Conference. April 4-10, 1986. Sarasota, Florida.
5. Human Papillomaviruses and Cervical Carcinoma. Second International Conference. October 27-29, 1986. Chicago, Illinois.
6. Human Papillomaviral Infection and Lower Genital Tract Neoplasia. May 7-9, 1987. Atlanta, Georgia.
7. HPV Workshop - Type Consensus Meeting. March 22-23, 1988. New York, New York.
8. Human Papillomaviruses and Squamous Carcinoma. Third International Conference. October 24-26, 1988. Chicago, Illinois.
9. Impact of HPV Testing on Cervical Cancer Screening and Diagnosis. National Cancer Institute Sponsored Conference. February 2, 1989. Rockville, Maryland.
10. Colposcopy, Cervical and Vulvar Pathology and Gynecologic Laser Surgery Conference. February 27-March 5, 1989. Sarasota, Florida.
11. UCLA Conference on Papillomaviruses. March 11-18, 1989. Taos, New Mexico.
12. An Update: Human Papillomavirus Infection. April 14, 1989. Lenexa, Kansas.
13. Fifth Annual Clinical Virology Symposium. April 30-May 3, 1989. Clearwater Beach, Florida.
14. Thirtieth Annual Meeting of the Japanese Clinical Cytology Society. June 14-16, 1989. Tokyo, Japan.
15. Colposcopy, Cervical and Vulvar Pathology and Gynecologic Laser Surgery Conference. November 5-12, 1989. Sarasota, Florida.
16. Human Papillomavirus Infections—A Postgraduate Course. October 21-22, 1989. Washington, DC.
17. Diagnosis and Treatment of Vulvar, Vaginal and Cervical Disease - A Postgraduate Course. October 27-28, 1989. Washington, DC.
18. National Meeting of the Canadian Association for Clinical Microbiology and Infectious Diseases. November 26-30, 1989. Montreal, Canada.
19. Workshop on Development of STD Diagnostics for Resource-Poor Settings. February 7-8, 1990. Rosslyn, Virginia.
20. Sixth Meeting of the Scandinavian Society for Gynecological Medicine. September 6-8th, 1990. Mariehamn, Finland.
21. International Symposium on Diagnosis of Sexually Transmitted Diseases. August 16-17, 1991. Uppsala, Sweden.
22. Fourth International Conference on Human Papillomaviruses and Genital Carcinoma. September 17-19, 1990. Chicago, Illinois.
23. Second IARC Workshop on HPV and Cervical Cancer, November 25-28, 1991. Brussels, Belgium.
24. Fifth International Conference on Human Papillomavirus. October 25-28, 1992. Chicago, Illinois.
25. St. Joseph's Institute of Laboratory Medicine Symposium. April 29, 1993. London, Ontario, Canada.
26. Twelfth Annual High Technology R&D Trade Fair. May 10-11, 1993. Arlington, Virginia.
27. 8th World Congress of Cervical Pathology and Colposcopy. May 12-16, 1993. Chicago, Illinois.
28. 1993 U.K. Wellcozyme Users Conference. June 17-18, 1993. St. Albans, England.

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29. Steering Committee Meeting of the International Biological Study on Cervical Cancer. October 2, 1993. Baltimore, Maryland.
30. The American Society for Colposcopy and Cervical Pathology, in joint sponsorship with The Society of Canadian Colposcopists. March 22-26, 1994. Orlando, Florida.
31. 2nd International Congress of Papillomavirus in Human Pathology. April 6-8, 1994. Paris, France.
32. Novel Amplification Technologies for DNA/RNA-Based Diagnostics. April 20-22, 1994. San Francisco, California.
33. First Congress on Papillomavirus of the Catholic Cancer Center. May 7, 1994. Seoul, Korea.
34. The Feasibility of Genetic Technology to Close the HIV Window in Donor Screening (US FDA workshop) September 26-28, 1994. Silver Spring, Maryland.
35. Nucleic Acid-Based Technology: Revolution in Clinical Diagnosis, Applications and Research. November 7-9, 1994. Amsterdam, The Netherlands.
36. Nucleic Acid-Based Technologies: Current Challenges, Future Strategies, and End User Perspectives. May 31-June 2, 1995. San Francisco, California.
37. Murex Users' Meeting. June 7-8, 1995. London, United Kingdom.
38. Eleventh Meeting of the International Society for STD Research, August 27-30, 1995. New Orleans, Louisiana.
39. X Congresso Brasileiro - II Congresso Latino Americano de Patologia do Trato Genital Inferior e Colposcopia. September 20-24, 1995. Sao Paulo, Brazil.
40. Workshop organized by Murex Diagnostica GmbH. October 12, 1995. Zurich, Switzerland.
41. XVth Asian and Oceanic Congress of Obstetrics and Gynecology. October 15-20, 1995. Bali, Indonesia.
42. Gene Quantification: Diagnosis, Monitoring & Drug Development. February 26-27, 1996. San Diego, California.
43. VIII Curso Internacional de Cancer Cervico Uterino y Lesiones Premalignas. March 7-9, 1996. Mexico City, Mexico.
44. Gene Detection: Diagnostic Technology for Infectious Agents and Human Genetic Diseases. May 2-3, 1996. Coronado, California.
45. 9th World Congress of Cervical Pathology and Colposcopy. May 12-16, 1996. Sydney, Australia.
46. EUROGIN-WHO International Joint Experts Meeting "Cervical Cancer Screening and New Developments. June 17-19, 1996. Geneva, Switzerland.
47. State of Maryland Department of Health and Mental Hygiene Office of Maternal Health and Family Planning. August 9, 1996. Annapolis, MD.
48. Advances in Nucleic Acid Amplification & Detection. September 18-19, 1996. Amsterdam, The Netherlands.
49. IV Simposio Internacional e III Jornada Baiana de Patologia do Trato Genital Inferior e Colposcopia. October 3-6, 1996. Salvador, Brazil.
50. The American Society for Microbiology, New York City Branch, & St. John's University. November 1, 1996. Jamaica, New York.
51. XIII Latin American Microbiology Congress. November 5-9, 1996. Caracas, Venezuela.
52. Workshop on Cervical Cancer Screening Program. November 6-7, 1996. Juquei, SP, Brazil.
53. EUROGIN-WHO 3rd International Congress on Lower Genital Tract Infections and Neoplasia: Future Challenges and Strategies. March 25-28, 1997. Paris, France.
54. 15th Annual Reproductive Health Update, co-sponsored by the Maryland Department of Health and Mental Hygiene Office of Maternal Health and Family Planning, Anne Arundel Community College, and Planned Parenthood. April 25, 1997. Arnold, MD.
55. Symposium on HPV Infection and Cervical Cancer. May 11, 1997. Seoul, Korea.
56. HPV workshop. May 16, 1997. Taipei, Taiwan, R.O.C.
57. XV FIGO World Congress of Gynecology and Obstetrics. August 3-8, 1997. Copenhagen, Denmark.

58. HPV Testing: European Perspectives on Cervical Neoplasia Prevention, Prognosis and Management. November 13-15, 1997. Geneva, Switzerland.
59. European HPV Clinical Summit Meeting. January 29-30, 1998. Vienna, Austria.
60. IV Reunión Nacional de Colposcopia y Patología Cervical. February 19-21, 1998. Guadalajara, Mexico.
61. Gene Quantification: Clinical Applications and Drug Development. March 30-April 1, 1998. San Diego, CA.
62. Biennial Meeting, American Society for Colposcopy and Cervical Pathology. March 30-April 2, 1998. Scottsdale, AZ.
63. ASCP/CAP Spring Meeting. April 4-8, 1998. Los Angeles, CA.
64. 8th European Course on HPV-Associated Pathology. April 22-24, 1998. Munich, Germany.
65. DNA/RNA Diagnostics. May 19-21, 1998. Washington, DC.
66. Microbial-Linked Diseases: Shifting the Pathogenic Paradigm. June 25-26, 1998. San Diego, CA.
67. Human Papillomavirus Infections and Cervical Cancer. July 7-11, 1998. Montreal, Canada.
68. Simposio Internacional sobre HPV: IV Curso de Atualizacao em Patologia do Trato Genital Preparatorio para Concurso de Qualificacao em Colposcopia. September 3-4, 1998. Belo Horizonte, Brazil.
69. III^{er} Congreso Latinoamericano y II^{do} Congreso Paraguayo de Patologia del Tracto Genital Inferior y Colposcopia. September 7-11, 1998. Asuncion, Paraguay.
70. 17th International Papillomavirus Conference. January 9-15, 1999. Charleston, SC.
71. INCCG - Consensus Conference on Cervical Cancer Screening and Management. January 28-31, 1999. Tunis, Tunisia.
72. HPV Summit 1999: New Approaches to the Detection and Elimination of Cervical Cancer. February 8-10, 1999. Chamonix, France.
73. Centers for Disease Control and Prevention and American Cancer Society External Consultants' Meeting: Prevention of Genital HPV Infection and Sequelae. April 13-14, 1999. Atlanta, GA.
74. 11th International Meeting of Gynaecological Oncology. May 8-12, 1999. Budapest, Hungary.
75. 4th Scientific Meeting on Primary and Secondary Prevention of Gynecological Cancer. May 14-16, 1999. Thessaloniki, Greece.
76. 13th Meeting of the International Society for Sexually Transmitted Diseases Research. July 11-14, 1999. Denver, CO.
77. Reproductive Health '99. September 22-25, 1999. New York, NY.
78. 1999 ASCP/CAP Fall Meeting. September 25-30, 1999. New Orleans, LA.
79. 10th World Congress of Cervical Pathology & Colposcopy. November 7-11, 1999. Buenos Aires, Argentina.
80. North American Sexual Health Management Symposium. November 21-23, 1999. New York, NY.
81. Cervical and Breast Cancer in the Next Millenium. December 3-6, 1999. Mexico City, Mexico.
82. XI Encontro de Atualização em Patologia do Trato Genital Inferior e Colposcopia - Cervicop' 2000. March 23-25, 2000. Sao Paulo, Brazil.
83. EUROGIN 2000: Global Challenge of Cervical Cancer Prevention. April 4-9, 2000. Paris, France.
84. ASCP/CAP Spring Meeting. April 9-12, 2000. Boston, MA.
85. Clinical Implications Conference 1: "Role of Human Papillomavirus in Cervical Neoplasia." April 28-29, 2000. Chicago, IL.
86. 26th National Meeting of the Clinical Ligand Assay Society. May 31-June 2, 2000. Boston, MA.
87. Meeting of the Pathological Society of Great Britain and Ireland. July 12-14, 2000. Nottingham, UK.
88. 7th International Meeting of Genital Tract Pathology & Colposcopy. October 25-30, 2000. Belo Horizonte, Brazil.

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Attachment C

INVITED SPEAKER
DEPARTMENTAL SEMINARS

1. Heidelberg Cancer Research Center, Heidelberg, Germany, November, 1985.
2. Columbia Hospital for Women, Washington, DC, December, 1985, 1986, and 1991.
3. Fred Hutchinson Cancer Research Center, Seattle, Washington, July, 1988.
4. Johns Hopkins Medical Institutions, Baltimore, Maryland, November, 1990.
5. University of New Hampshire, Department of Microbiology, October, 1991.
6. Sharp Memorial Hospital OB/GYN Department, San Diego, California, November 11, 1993.
7. Prodia Laboratory, Jakarta, Indonesia, May 3, 1994.
8. Bio-Check Laboratories Ltd. Pathology, Diagnostic Virus, and Gynecology Departments, Taipei, Taiwan, R.O.C., May 5, 1994.
9. University College Hospital Virology Department, London, United Kingdom, June 16, 1995.
10. John Radcliffe Infirmary Pathology Department, Oxford, United Kingdom, June 17, 1995.
11. National Cancer Hospital Cytology Department, Oslo, Norway, October 10, 1995.
12. Columbia Hospital for Women Pathology Department, Washington, DC, October 24, 1995.
13. Associated Regional University Pathologists (ARUP), Salt Lake City, UT, February 28, 1996.
14. Washington Hospital Center, Transplant Surgery Department, March, 1996.
15. Health Insurance Plan of New York, Jericho, NY, April 24, 1996.
16. Friedrich Schiller University Department of Obstetrics and Gynecology, Jena, Germany, May 8, 1996.
17. Unilab KPT/ Murex Diagnostica GmbH, HPV workshop for gynecologists/venerologists/pathologists/virologists, Budapest, Hungary, May 10, 1996.
18. Long Island Jewish Medical Center Gynecology Department, New York, NY, June 5, 1996.
19. Washington Gynecological Society, Washington, DC, January 8, 1997.
20. Hyundai Medical Center, Seoul, Korea, May 10, 1997.
21. Seoul National University, Seoul, Korea, May 12, 1997.
22. Papanicolaou Institute, Buenos Aires, Argentina, July 14-16, 1997.
23. Doctors' meeting convened by Murex Central Europe, Vienna, Austria, November 17, 1997.
24. One seminar and one grand rounds, for the departments of Gynecologic Oncology, Biochemistry & Molecular Genetics, and Infectious Diseases at the University of Alabama at Birmingham, December 9-10, 1998.
25. Maryland Bioscience Alliance, High Technology Council of Maryland, Rockville, MD, January 21, 1999.
26. University of Rochester Research Symposium on Human Papillomavirus Infections from the Bench to the Bedside, Rochester, NY, April 30, 1999.
27. Women's Health Task Force Meeting, Washington, DC, February 29-March 1, 2000.
28. Maryland Bioscience Alliance Cancer Forum, High Technology Council of Maryland, Rockville, MD, March 22, 2000.
29. Gynecologic Cancer Translational Research Retreat, Chantilly, VA, May 5-6, 2000.
30. 18th Annual Reproductive Health Update for the Maryland Department of Health, Annapolis, MD, May 19, 2000.
31. Georgetown University Department of Pathology, Washington, DC, May 25, 2000.
32. Cleveland Clinic Foundation, Cleveland, OH, June 30, 2000.

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33. University of Medicine and Dentistry of New Jersey, Scotch Plains, NJ. October 13, 2000.